Claims

We claim:

1. An antibody that competes with one or more of the antibodies listed in Tables 2 and 3 (SEQ ID NO: 1-60) for binding to a plurality of different hemagglutinin (HA) polypeptides, which plurality of different HA polypeptides includes HA polypeptides proteins found in at least 2 different HA subtypes.

2. The antibody of claim 1, wherein the antibody comprises one or more complementarity determining regions (CDRs) or one or more framework region (FRs) that is identical in sequence to a corresponding CDR or FR from Tables 2 and 3 (SEQ ID NO: 1-60).

3. An antibody comprising one or more CDRs or one or more FRs that is at least 80% identical in sequence to a corresponding CDR or FR from Tables 2 and 3 (SEQ ID NO: 1-60).

4. An antibody comprising CDR and FR sequences that together contain no more than 18 substitutions as compared with corresponding CDR and FR sequences from Tables 2 and 3 (SEQ ID NO: 1-60).

5. An antibody comprising CDR and FR sequences that together contain no more than 15 substitutions as compared with corresponding CDR and FR sequences from Tables 2 and 3 (SEQ ID NO: 1-60).

6. The antibody of any one of the preceding claims, wherein the antibody comprises a complementarity determining region (CDR) 1 that shows at least 65%, more than 70%, more than 75%, more than 80%, more than 85%, more than 90%, more than 95%, or more than 99% identity with CDR1 regions from Tables 2 and 3 (SEQ ID NOs:17-18 and/or SEQ ID NOs:44-54).

7. The antibody of any one of the preceding claims, wherein the antibody comprises a complementarity determining region (CDR) 1 that has at least two amino acid substitutions as

compared to CDR1 regions from Tables 2 and 3 (SEQ ID NOs:17-18 and/or SEQ ID NOs:44-54).

8. The antibody of any one of the preceding claims, wherein the antibody comprises a complementarity determining region (CDR) 1 that has fewer than two amino acid substitutions as compared to CDR1 regions from Tables 2 and 3 (SEQ ID NOs:17-18 and/or SEQ ID NOs:44-54).

9. The antibody of any one of the preceding claims, wherein the antibody comprises a complementarity determining region (CDR) 1 that has an amino acid sequence that is identical to that of one of the CDR1 regions from Tables 2 and 3 (SEQ ID NOs:17-18 and/or SEQ ID NOs:44-54).

10. The antibody of any one of the preceding claims, wherein the antibody comprises a complementarity determining region (CDR) 2 that shows at least 65%, more than 70%, more than 75%, more than 80%, more than 85%, more than 90%, more than 95%, or more than 99% identity with CDR2 regions from Tables 2 and 3 (SEQ ID NOs:19-20 and/or SEQ ID NOs:55-58).

11. The antibody of any one of the preceding claims, wherein the antibody comprises a complementarity determining region (CDR) 2 that has at least two amino acid substitutions as compared to CDR2 regions from Tables 2 and 3 (SEQ ID NOs:19-20 and/or SEQ ID NOs:55-58).

12. The antibody of any one of the preceding claims, wherein the antibody comprises a complementarity determining region (CDR) 2 that has fewer than two amino acid substitutions as compared to CDR2 regions from Tables 2 and 3 (SEQ ID NOs:19-20 and/or SEQ ID NOs:55-58).

13. The antibody of any one of the preceding claims, wherein the antibody comprises a complementarity determining region (CDR) 2 that has an amino acid sequence that is identical to that of one of the CDR2 regions from Tables 2 and 3 (SEQ ID NOs:19-20 and/or SEQ ID NOs:55-58).

14. The antibody of any one of the preceding claims, wherein the antibody comprises a complementarity determining region (CDR) 3 that shows at least 65%, more than 70%, more than 75%, more than 80%, more than 85%, more than 90%, more than 95%, or more than 99% identity with CDR3 regions from Tables 2 and 3 (SEQ ID NOs:21-32 and/or SEQ ID NOs:59-60).

15. The antibody of any one of the preceding claims, wherein the antibody comprises a complementarity determining region (CDR) 3 that has at least two amino acid substitutions as compared to CDR3 regions from Tables 2 and 3 (SEQ ID NOs:21-32 and/or SEQ ID NOs:59-60).

16. The antibody of any one of the preceding claims, wherein the antibody comprises a complementarity determining region (CDR) 3 that has fewer than two amino acid substitutions as compared to CDR3 regions from Tables 2 and 3 (SEQ ID NOs:21-32 and/or SEQ ID NOs:59-60).

17. The antibody of any one of the preceding claims, wherein the antibody comprises a complementarity determining region (CDR) 3 that has an amino acid sequence that is identical to that of one of the CDR3 regions from Tables 2 and 3 (SEQ ID NOs:21-32 and/or SEQ ID NOs:59-60).

18. The antibody of any one of the preceding claims, wherein the antibody comprises a VH framework region that shares more than 65%, more than 70%, more than 75%, more than 80%, more than 85%, more than 90%, more than 95%, or more than 99% percent identity with a VH framework region from Table 2 (SEQ ID NOs:1-16).

19. The antibody of any one of the preceding claims, wherein the antibody comprises a VL framework region of the present invention will share more than 65%, more than 70%, more than 75%, more than 80%, more than 85%, more than 90%, more than 95%, or more than 99% percent identity with a VL framework region from Table 3 (SEQ ID NOs:33-43).

20. The antibody of any one of the preceding claims, wherein the antibody shows binding to influenza HA selected from the group consisting of group 1 subtype, group 2 subtype, and combinations thereof.

21. The antibody of any one of the preceding claims, wherein the antibody shows neutralization IC50 (ug/ml) of influenza HA selected from the group consisting of group 1 subtype, group 2 subtype, and combinations thereof.

22. The antibody of any one of the preceding claims, wherein the antibody binds to at least one HA polypeptides of subtype selected from the group consisting of H1, H2, H3, H4, H5, H6, H7, H8, H9, H10, H11, H12, H13, H14, H15, H16, and combinations thereof.

23. The antibody of claim 22, wherein the antibody binds to at least two of HA polypeptides of subtype selected from the group consisting of H1, H3, H5, H7, H9, and combinations thereof.

24. The antibody of any one of the preceding claims, wherein the antibody is an IgG.

25. The antibody of any one of the preceding claims, wherein the antibody is a monoclonal antibody.

26. The antibody of any one of the preceding claims, wherein the antibody is selected from the group consisting of human antibody, mouse antibody, rabbit antibody, and combinations thereof.

27. The antibody of any one of the preceding claims, wherein the antibody is a human antibody.

28. An antibody comprising any one of VH-1, VH-2, VH-3, VH-4, VH-5, VH-6, VH-7, VH-8, VH-9, VH-10, VH-11, VH-12, VH-13, VH-14, VH-15, VH-16 or fragment thereof combined with any one of VL-1, VL-2, VL-3, VL-4, VL-5, VL-6, VL-7, VL-8, VL-9, VL-10, VL-11, or fragment thereof.

29. The antibody of claim 28, wherein the antibody has VH-1 (SEQ ID NO:1) combined with VL-1 (SEQ ID NO:33).

30. A binding agent whose structure includes one or more features of an antibody as set forth in any one of claims 1-29, such that the binding agent shows an IC_{50} (ug/ml) for an influenza virus selected from the group consisting of group 1 subtype, group 2 subtype, and combinations thereof.

31. A binding agent whose structure includes one or more features of an antibody as set forth in any one of claims 1-29, such that the binding agent shows binding to an influenza HA with a K_D less than 2000nM, less than 1500nM, less than 1000nM, less than 500nM, less than 250nM, less than 225nM, less than 200nM, less than 175nM, less than 150nM, less than 125nM, less than 100nM, less than 75nM, or less than 50nM.

32. A binding agent whose structure includes one or more features of an antibody as set forth in any one of claims 1-29, such that the binding agent shows binding to an influenza HA with a K_a whose lower bound is about $0.01x10^5$ $M^{-1}s^{-1}$and upper bound is about $1.0x10^6$ $M^{-1}s^{-1}$.

33. A binding agent whose structure includes one or more features of an antibody as set forth in any one of claims 1-29, such that the binding agent shows binding with a K_d whose lower bound is about $0.01x10^5$ $s^{-1}$and upper bound is about $1.0x10^6$ s^{-1}.

34. The binding agent of any one of claims 30-33, wherein the binding agent comprises a polypeptide.

35. The polypeptide of claim 34, wherein the polypeptide comprises at least one amino acid that is PEGylated.

36. The polypeptide of claim 34, wherein the polypeptide comprises at least one amino acid that is glycosylated.

37. The polypeptide of claim 34, wherein the polypeptide comprises an antibody.

38. The antibody of claim 37, wherein the antibody comprises an antibody fragment.

39. The antibody of claim 37, wherein the antibody is conjugated to a natural polymer selected from the group consisting of albumin, chitosan, heparin, paclitaxel, poly-(L-glutamate), N-(2-hydroxypropyl)methacrylamide (HPMA), poly-(L-lactide) (PLA), poly(amidoamine) (PAMAM), folate and~~/or~~ combinations thereof.

40. The binding agent of any one of claims 30-33, wherein the binding agent comprises a stapled peptide.

41. The binding agent of any one of claims 30-33, wherein the binding agent comprises a scaffold protein.

42. The scaffold protein of claim 41, wherein the scaffold protein is selected from the group consisting of fibronectin, lipocalin, anticalin, protein, thioredoxin A, ankyrin repeat, armadillo repeat, tetratricopeptide repeat and combinations thereof.

43. The binding agent of any one of claims 30-33, wherein the binding agent comprises a mini-antibody.

44. The binding agent of any one of claims 30-33, wherein the binding agent comprises a peptidomimetic.

45. The binding agent of any one of claims 30-33, wherein the binding agent comprises a mimotope.

46. A cell line expressing the antibody of any one of claims 1-29.

47. The cell line of claim 46, wherein the cell line is a mammalian cell line.

48. The cell line of claim 46, wherein the cell line is a hybridoma.

49. A pharmaceutical composition comprising:.
an antibody selected from any one of claims 1-29; and;
a pharmaceutically acceptable excipient.

50. A pharmaceutical composition comprising:

a binding agent that recognizes an epitope recognized by an antibody selected from any one of claims 1-29; and;

a pharmaceutically acceptable excipient.

51. A pharmaceutical composition comprising:

a fragment of an antibody selected from any one of claims 1-29, wherein the fragment retains the antigen binding activity of the whole antibody; and

a pharmaceutically acceptable excipient.

52. The pharmaceutical composition of any one of claims 49-51, further comprising at least one additional antiviral agent.

53. Use of a therapeutically effective amount of the antibody, binding agent or pharmaceutical composition of any one of claims 1-29, 30-45, and 49-52, in the manufacture of a medicament for treating a subject suffering from or susceptible to influenza infection.

54. A kit comprising:

at least one antibody of any one of claims 1-29;

a syringe, needle, or applicator for administration of the at least one antibody to a subject; and

instructions for use.

55. A kit comprising:

at least one binding agent of any one of claims 30-45;

a syringe, needle, or applicator for administration of the at least one antibody to a subject; and

instructions for use.

Claims

1. A composition comprising: an engineered polypeptide that has an amino acid sequence comprising an immunoglobulin heavy chain variable region that contains no more than 16 substitutions as compared with the heavy chain variable region of SEQ ID NO: 1.

2. The composition of claim 1, further comprising a second polypeptide that has an amino acid sequence comprising an immunoglobulin light chain variable region.

3. The composition of claim 1, wherein the substitutions compared with the heavy chain variable region of SEQ ID NO: 1 include one or more of T30S, , S100T, S100D, S100G, E101N, E101K, E101Q, S104T, Q113S, Y115L, Y115F, F116L, N117D, P118Y or combinations thereof.

4. The composition of claim 1, wherein the heavy chain variable region contains no more than 10 substitutions as compared with the heavy chain variable region of SEQ ID NO: 1.

5. The composition of claim 1, wherein the heavy chain variable region contains no more than 6 substitutions as compared with the heavy chain variable region of SEQ ID NO: 1.

6. The composition of claim 1, wherein the heavy chain variable region shows more than 90% identity with the heavy chain variable region of SEQ ID NO: 1.

7. The composition of claim 6, having heavy chain CDRs that show more than 80% identity with the CDRs of SEQ ID NO: 1.

8. The composition of claim 6, having heavy chain CDRs that show more than 90% identity with the CDRs of SEQ ID NO: 1.

9. The composition of claim 1, having heavy chain CDRs that show more than 80% identity with the CDRs of SEQ ID NO: 1.

10. The composition of claim 1, having heavy chain CDRs that show more than 90% identity with the CDRs of SEQ ID NO: 1.

11. The composition of claim 1, having heavy chain CDRs that have fewer than 2 amino acid substitutions as compared with the CDRs of SEQ ID NO: 1.

12. The composition of claim 1, wherein the polypeptide binds to HA polypeptides of subtype H1, H3, H5, H7, H9.

13. The composition of claim 1, wherein the immunoglobulin heavy chain variable region comprises a heavy chain complementarity determining region (CDR) 1 that has fewer than two amino acid substitutions as compared to the CDR1 region from the heavy chain variable region of SEQ ID NO: 1.

14. The composition of claim 1, wherein the immunoglobulin heavy chain variable region comprises a heavy chain complementarity determining region (CDR) 1 that has an amino acid sequence that is identical to that of the CDR1 region of the heavy chain variable region of SEQ ID NO: 1.

15. The composition of claim 1, wherein the immunoglobulin heavy chain variable region comprises a heavy chain complementarity determining region (CDR) 2 that has fewer than two amino acid substitutions as compared to the CDR2 region of the heavy chain variable region of SEQ ID NO: 1.

16. The composition of claim 1, wherein the immunoglobulin heavy chain variable region comprises a heavy chain complementarity determining region (CDR) 3 that has fewer than two amino acid substitutions as compared to the CDR3 region of the heavy chain variable region of SEQ ID NO: 1.

17. The composition of claim 2, wherein the light chain variable region shows more than 70% identity with a light chain variable region of Table 3 SEQ ID NOs: 33-43.

18. The composition of claim 2, wherein the light chain variable region shows more than 75% identity with a light chain variable region of Table 3 SEQ ID NOs: 33-43.

19. The composition of claim 2, wherein the light chain variable region shows more than 80% identity with a light chain variable region of Table 3 SEQ ID NOs: 33-43.

20. The composition of claim 2, wherein the light chain variable region shows more than 85% identity with a light chain variable region of Table 3 SEQ ID NOs: 33-43.

21. The composition of claim 2, wherein the light chain variable region shows more than 90% identity with a light chain variable region of Table 3 SEQ ID NOs: 33-43.

22. The composition of claim 2, wherein the light chain variable region shows more than 95% identity with a light chain variable region of Table 3 SEQ ID NOs: 33-43.

23. The composition of claim 2, wherein the light chain variable region shows more than 70% identity with the light chain variable region of SEQ ID NO: 33.

24. The composition of claim 2, wherein the light chain variable region shows more than 75% identity with the light chain variable region of SEQ ID NO: 33.

25. The composition of claim 2, wherein the immunoglobulin heavy chain variable region comprises VH-1 (SEQ ID NO: 1) and the immunoglobulin light chain variable region comprises VL-1 (SEQ ID NO: 33).

26. The composition of claim 2, wherein the composition shows binding to influenza HA selected from the group consisting of group 1 subtype, group 2 subtype, and combinations thereof.

27. The composition of claim 2, wherein the composition shows neutralization IC_{50} (ug/ml) of influenza HA selected from the group of group 1 subtype, group 2 subtype, and combinations thereof.

28. The composition of claim 2, wherein the composition binds to at least two of HA polypeptides of subtype selected from the group of H1, H3, H5, H7, H9, and combinations thereof.

29. The composition of claim 2, wherein the engineered polypeptide and the second polypeptide together constitute an IgG.

30. The composition of claim 2, wherein the engineered polypeptide and the second polypeptide together constitute a monoclonal antibody.

31. The composition of claim 2, wherein the engineered polypeptide and the second polypeptide together constitute an antibody and the composition further comprises a pharmaceutically acceptable excipient.

32. A polypeptide whose amino acid sequence includes sequences corresponding to each of CDR1, CDR2, and CDR3 found in SEQ ID NO:33, which sequences are either identical to SEQ ID NO: 44, SEQ ID NO: 55 and SEQ ID NO: 59 or:

with respect to CDR1, differ from the CDR1 in SEQ ID NO: 33 due to a substitution compared with SEQ ID NO: 33 that includes Y31F; and

with respect to CDR3, differ from the CDR3 of SEQ ID NO: 33 due to a substitution compared with SEQ ID NO: 33 that includes Y95H.

33. An HA polypeptide binding agent comprising: an engineered polypeptide that has an amino acid sequence comprising: an immunoglobulin heavy chain variable region that contains no more than 16 substitutions as compared with the heavy chain variable region of SEQ ID NO: 1.

34. An engineered polypeptide whose heavy chain variable region amino acid sequence comprises CDR1 (SEQ ID NO: 17), CDR2 (SEQ ID NO: 19), and CDR3 (SEQ ID NO: 21).

35. The engineered polypeptide of claim 34, having heavy chain CDRs that contains no more than 2 amino acid substitutions as compared with the CDRs of SEQ ID NO: 1.

36. A binding agent that is or comprises a full-length antibody or fragment thereof, which binding agent comprises the polypeptide of claim 34, and binds to an HA antigen.

37. A heavy chain variable region that contains no more than 16 substitutions as compared with the heavy chain variable region of SEQ ID NO: 1.

38. The heavy chain variable region of claim 37, wherein the heavy chain variable region contains no more than 10 substitutions as compared with the heavy chain variable region of SEQ ID NO: 1.

39. The heavy chain variable region of claim 37, wherein the heavy chain variable region contains no more than 6 substitutions as compared with the heavy chain variable region of SEQ ID NO: 1.

40. The heavy chain variable region of claim 37, wherein the heavy chain variable region shows more than 90% identity with the heavy chain variable region of SEQ ID NO: 1.

41. The heavy chain variable region of claim 37, having heavy chain CDRs that show more than 80% identity with the CDRs of SEQ ID NO: 1.

42. The heavy chain variable region of claim 37, having heavy chain CDRs that show more than 90% identity with the CDRs of SEQ ID NO: 1.

43. The heavy chain variable region of claim 37, having heavy chain CDRs that have fewer than 2 substitutions as compared with the CDRs of SEQ ID NO: 1.

44. The heavy chain variable region of claim 40, having heavy chain CDRs that show more than 80% identity with the CDRs of SEQ ID NO: 1.

45. The heavy chain variable region of claim 40, having heavy chain CDRs that show more than 90% identity with the CDRs of SEQ ID NO: 1.

46. The heavy chain variable region of claim 40, having heavy chain CDRs that have fewer than 2 substitutions as compared with the CDRs of SEQ ID NO: 1.

47. A cell line expressing the engineered polypeptide of claim 1.

48. The cell line of claim 47, wherein the cell line is a mammalian cell line.

49. The cell line of claim 47, wherein the cell line is a hybridoma.

50. A kit comprising:

at least one composition of claim 2;

a syringe, needle, or applicator for administration of the at least one antibody to subject;

and

instructions for use.